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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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12/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,745	CASIMIR, COLIN MAURICE	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/14/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-45,47,48 and 50-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-45,47,48 and 50-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim amendments filed on 10/14/2009 have been received and entered. The Declaration signed by Colin M. Casimir filed on 10/14/2009 has been considered.

Claims 1-42, 46, 49, and 57-67 are cancelled. Claim 43 is amended. Claims 43-45, 47, 48 and 50-56 are pending and currently under examination.

This application 10/520,745 filed on Aug. 22, 2005 is a 371 of PCT/GB03/03012 filed on 07/11/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claims 43-45, 47, 48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because independent claim 43 has been amended.

Claim 43 has been amended to delete three "--" signs recite in step (ii).

Claim 43 has been amended to recite "(ii) expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane <u>of the package cell</u> and a viral particle buds from said packaging cell membrane".

With regard to whether the steps of claims 43 relate back to the preamble of claim 43, Applicant argues that the limitation "allowing the passenger peptide binding moiety to be

incorporated into viral particle to modify its first cell binding activity" recited in step (ii) of claim 43 does require "having a modified cell binding activity" recited in the preamble of claim 43. Upon further consideration, the limitations "having a modified cell binding activity" recite din the preamble and "to modify its first cell binding activity" recited in step (ii) of claim 43 are broad, but not in indefinite.

Claims 44, 45, 47, 48 and 50-56 depend from claim 43.

Claim Rejection – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous rejection of claims 43-45, 47, 48 and 50-56 under 35 U.S.C. 112, first paragraph, is ***withdrawn*** because the Declaration by the inventor, Colin M. Casmir, filed on 10/14/2009 provides enabling support for two additional peptide binding moieties other than a human stem cell factor (SCF) for the claimed methods. The declaration provides support for (i) targeted transduction of cell expressing macrophage colony stimulating factor (MCSF) receptor (c-fms) using virus displaying surface MCSF and (ii) targeted transduction of primary human T cells using virus displaying surface IL-2.

This withdrawn scope of enablement rejection documented that the specification, while being enabling for **(I)** a method of making a retroviral particle having a modified cell binding activity by genetically modifying envelope proteins of the retroviral particle, and enabling for **(II)** a method of making a retroviral particle having a modified cell binding activity without

genetically modifying envelope proteins of the retroviral particle, comprising the steps of providing a retroviral packaging cell, wherein the retroviral packaging cell contains viral nucleic acid encoding an enveloped viral particle that is unable to naturally bind to a target cell; and transfecting said retroviral packaging cell line with an expression vector comprising a heterologous nucleic acid sequences encoding a membrane bound human stem cell factor (mbSCF) operably linked to an eukaryotic promoter such that human mbSCF is expressed on the membrane of the packaging cell wherein a resulting retroviral particle produced from said packaging cell bears human mbSCF on the envelope of the retroviral particle that directs the binding of the retroviral particle to a target cell expressing c-kit on the membrane of said target cell, **does not** reasonably provide enablement the said method without genetically modifying envelope proteins of the retroviral particle [i.e. abovementioned **(II)**] for **(i)** a nucleic acid encoding any peptide binding moiety other than a human stem cell factor (SCF), or **(ii)** any target cell other than the target cell expressing c-kit receptor on its cell membrane, or **(iii)** a method comprising steps of making a retroviral particle having a modified cell binding activity, wherein the modified cell binding activity of said retroviral particle is determined by any non-Envelope-receptor interactions.

Claim Rejection – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 43-45, 54, and 55 remain rejected under 35 U.S.C. 102(a) as being anticipated by Gollan et al., Redirecting retroviral tropism by insertion of short, non-disruptive peptide ligands into envelope, *J Virol.* 76(7):3558-63, 2002). Applicant's arguments filed 10/14/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-15 of the office action mailed on 04/14/2009.

For the clarity and completeness of this office action, the rejection is ***maintained*** for the reasons of record advanced on pages 14-15 of the office action mailed on 04/14/2009, is reiterated below with editorial revisions addressing claim amendments filed on 10/14/2009.

Amended claim 43 filed on 10/14/2009 reads as follows: A method of making a viral particle having a modified cell binding activity comprising:

(i) providing a viral packaging cell containing viral nucleic acid encoding an enveloped viral particle, wherein said viral particle is enveloped using an envelope unable to naturally bind to cells of a species being targeted, said viral particle having a first cell binding activity wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety designed to modify said first cell binding activity of said viral particle;

(ii) expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane of the packaging cell and a viral particle buds from said packaging cell membrane thereby allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity, wherein the passenger peptide binding moiety is selected from the group consisting of cell growth factors, antibodies or antigen-binding fragments thereof, moieties that recognize a target cell specific surface antigen, and moieties that are at least a part of a member of a binding pair comprising a target cell specific cell surface receptor and its ligand

and wherein said passenger peptide is other than one naturally derived from the virus or said packaging cell.

Claim interpretation: The limitation "wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety" recited in step (i) of claim 43 reads on any viral genome because the viral genomic nucleic acids are exogenous to the endogenous genomic DNA of the viral packaging cell. The interpretation that the breadth of claim 43 encompasses any viral genome encoding claimed "passenger peptide" is supported by claim 56, which recites further limitation "wherein the modified cell binding activity is conferred by a peptide other than a chimeric viral envelopes polypeptide".

With regard to the limitations of claim 43, 45, 54, and 55, Gollan et al. teaches that potentially powerful approach for *in vivo* gene delivery is to target retrovirus to specific cells through interactions between cell surface receptors and appropriately modified viral envelope proteins. Gollan et al. teaches that, relatively large (>100 residues) protein ligands to cell surface receptors have been inserted at or near the N terminus of retroviral envelope proteins; and although viral tropism could be altered, the chimeric envelope proteins lacked full activity, and coexpression of wild-type envelope is required for production of transducing virus. Gollan et al. analyzes more than 40 derivatives of ecotropic Moloney murine leukemia virus (MLV) envelope, containing insertions of short RGD-containing peptides, which are ligands for integrin receptors, and in many cases pseudotyped viruses containing only the chimeric envelope protein could transduce human cells. Gollan et al. teaches that the precise location, size, and flanking sequences of the ligand affected transduction specificity and efficiency, and concludes that retroviral tropism can be rationally reengineered by insertion of short peptide ligands and without the need to coexpress wild-type envelope (See abstract, Gollan et al., Selective targeting

and inducible destruction of human cancer cells by retroviruses with envelope proteins bearing short peptide ligands, *J Virol.*, 76(7):3564-9, 2002).

With regard to the limitation of claim 44 reciting "the peptide binding moiety is provided at an outer plasma membrane of the cell", it is noted that during the process of viral budding from the packaging cell the viral envelope proteins are provided at the outer membrane of the packaging cell.

Thus, Gollan et al. clearly anticipates claims 43-45, 54, and 55 of instant application.

Applicant's arguments

Applicant argues that Gollan et al. is not believed to provide any teaching that represents a rational or predictable approach to cell modification. Applicant argues that Gollan et al. appears to make insertions at random in the envelope and thereafter test for any changed properties, rather than presenting a systematic approach. Most of the modifications they make inactivate the envelope protein, or compromise it in some way. Applicant argues that Gollan et al. has no way of predicting the outcome of the modifications until they are tested and the method requires the experimenter to make a very large number of modifications to pick up any with altered properties. This approach cannot be used to make changes of a predictable nature and is therefore of limited applicability, especially as it is clear that none of the envelope modifications can be made without some compromise to its function and its functional efficiency (See pages 8-9 of Applicant's reply filed on 10/14/2009).

Response to Applicant's arguments

It is noted that claim 43 as written only requires "a modified cell binding activity" recited in the preamble of claim 43 and "passenger peptide binding moiety to be incorporated into the viral particle to modify its first binding activity" recited in step (ii) of claim 43. There is no requirement specified what "a first cell binding activity" is and how "a first cell binding activity" is modified. Thereby, Gollan et al. teaches all the limitations of claims 43-45, 54, and 55 and thereby anticipates claims 43-45, 54, and 55 of instant application.

Related to the breadth of claimed methods, it is worth noting that Applicant states on pages 7-8 of Applicant's reply filed on 10/14/2009 that "In addition to the Declaration and accompanying data, the Examiner is asked to consider also the work of Baltimore and Wang (*PNAS*, 103(31): 11479-11484, 2006), attached hereto as Exhibit A, which, applicant believes, has shown that other skilled practitioners in the art have clearly been able to readily pick up on the work described in the present specification and adopt it to their own needs. They have substituted ecotropic envelope with a mutant form of spleen necrosis virus envelope (not a retrovirus incidentally) to make targetable lentiviruses. They were successful in this with SCF (though this has just only just been published), but have additionally used CD20 and antibody for specific targeting. One aspect that these authors have picked up on, which is an idea first raised by the present inventor in a paper in Blood in 2004 (Chandrashekran et al, 104(9):2697-2703, 2004), attached hereto as Exhibit B, is the separation of binding and fusion functions to two separate molecules".

The Examiner notes that the approach by Yang et al. [i.e. the work of Baltimore and Wang (*PNAS*, 103(31): 11479-11484, 2006), as Applicant stated] is constructing a fusogen by modifying viral envelope proteins to alter the tropism of lentivirus and to target the lentivirus to a

specific cell type. Modifications in envelope changing the tropism of the viral particles is the approach shared between the teachings by Gollan et al. (*J Virol.* 76(7):3558-63, 2002) and by Yang et al. (*PNAS*, 103(31): 11479-11484, 2006), and this approach/method is certainly encompassed by the claimed methods as Applicant's statements clearly indicate.

4. Claims 43-45, 47, and 54-56 remain rejected under 35 U.S.C. 102(b) as being anticipated by **Povey et al.** (Povey et al., Enhanced retroviral transduction of 5-fluorouracil-resistant human bone marrow (stem) cells using a genetically modified packaging cell line, *Blood*, 92(11):4080-9, 1998) as evidenced by **Hammarstedt et al.** (Hammarstedt et al. Minimal exclusion of plasma membrane proteins during retroviral envelope formation. *Proc Natl Acad Sci U S A.* 97(13):7527-32, 2000; this reference has been provided as Exhibit A in the Applicant's remarks filed on 05/20/2008). Applicant's arguments filed 10/14/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 15-18 of the office action mailed on 04/14/2009.

For the clarity and completeness of this office action, the rejection is ***maintained*** for the reasons of record advanced on pages 15-18 of the office action mailed on 04/14/2009, is reiterated below with editorial revisions addressing claim amendments filed on 10/14/2009.

Amended claim 43 filed on 10/14/2009 reads as follows: A method of making a viral particle having a modified cell binding activity comprising:

(i) providing a viral packaging cell containing viral nucleic acid encoding an enveloped viral particle, wherein said viral particle is enveloped using an envelope unable to naturally bind to cells of a species being targeted, said viral particle having a first cell binding activity wherein

the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety designed to modify said first cell binding activity of said viral particle;

(ii) expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane of the packaging cell and a viral particle buds from said packaging cell membrane thereby allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity, wherein the passenger peptide binding moiety is selected from the group consisting of cell growth factors, antibodies or antigen-binding fragments thereof, moieties that recognize a target cell specific surface antigen, and moieties that are at least a part of a member of a binding pair comprising a target cell specific cell surface receptor and its ligand and wherein said passenger peptide is other than one naturally
derived from the virus or said packaging cell.

Claim interpretation: The limitation "wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety" reads on any extra-chromosomal nucleic acid introduced into a given viral packaging cell because extra-chromosomal nucleic acids are exogenous to the endogenous genomic DNA of the viral packaging cell.

Povey et al. teaches constructed a retroviral producer line (1MI-ΔSCF) that expresses the membrane-bound form of human stem cell factor (SCF) on its cell surface (See bridging paragraph, pages 4081-4082, and Figure 1, provided below, Povey et al., *Blood*, 92(11):4080-9, 1998).

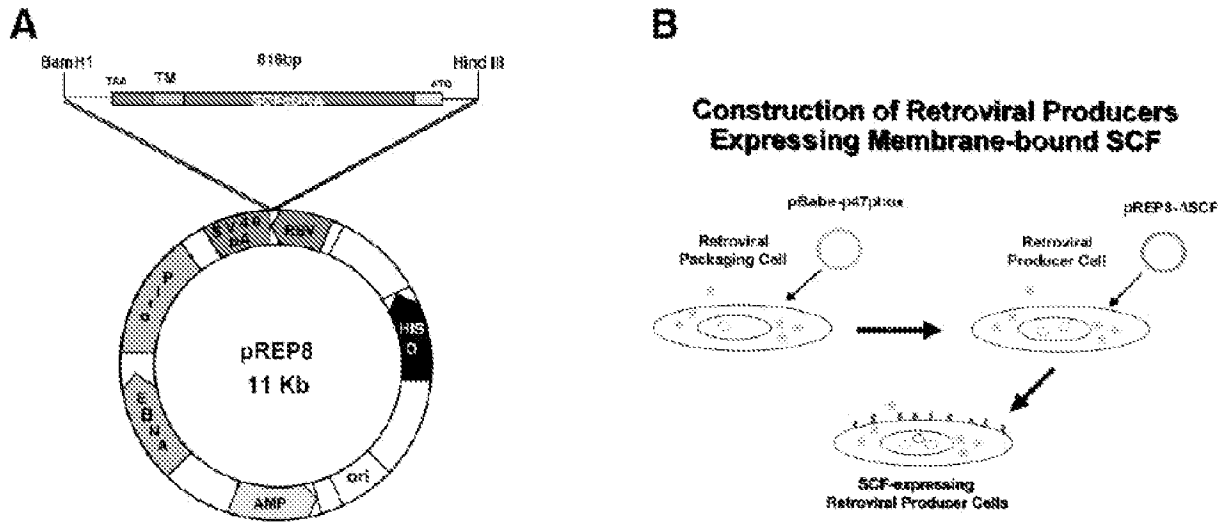

Fig 1. Construction of retroviral producer cells expressing membrane-bound SCF. (A) Schematic of plasmid pREP8-ΔSCF. (B) Evolution of cell line 1MI-ΔSCF from AM12 packaging line.

Povey et al. the retroviral transduction frequency of the quiescent 5-fluorouracil (FU) resistant bone marrow cells using the SCF-expressing producer line averaged about 20%, whereas those transduced using the retroviral particle obtained from parent producer line showed evidence of reduced levels or no transduction (See page 4084 and Figure 3, Povey et al., *Blood*, 92(11):4080-9, 1998).

Povey et al. does not explicitly teach that the SCF (i.e. a passenger peptide binding moiety encoded by exogenous nucleic acid, encompassed by claim 43 of instant application) is allowed to be incorporated into the viral particle, which in turn may account, at least in part, for the increased retroviral transduction frequency using the SCF-expressing producer line.

However, Hammarstedt et al. teaches that the retrovirus forms its envelope by budding at the plasma membrane (PM), and this process is primarily driven by its cytoplasmic core-precursor protein, Gag, as shown by the efficient formation of virus-like Gag particles in the absence of its envelope protein, Env. Hammarstedt et al. teaches the purification of Moloney murine leukemia virus Gag particles by sedimentation in an iodixanol gradient and donor PMs

by flotation in a sucrose gradient and compared their protein compositions at equal lipid basis, and found that most PM proteins are present at similar density in both membranes. Hammarstedt et al. teaches the inclusion of PM proteins was unaffected by incorporation of Env protein into the envelope of the Gag particles and whether these were produced at high or low level in the cells. Hammarstedt et al. concludes that these findings indicate that plasma membrane (PM) proteins become incorporated into the retrovirus envelope without significant sorting, and this feature of retrovirus assembly should be considered when studying retrovirus functions and developing retrovirus vectors.

The teachings by Hammarstedt et al. clarify that the retroviral particles produced from the SCF-expressing producer line taught by **Povey et al.** will inherently allow the SCF, which is expressed on the plasma membrane of the retroviral packaging cell, to be incorporated into the retroviral particles when the viral particle buds from the retroviral packaging cell, as recited in claim 43 of instant application.

Thus, Povey et al. as evidenced by Hammarstedt et al. clearly anticipates claims 43-45, 47, and 54-56 of instant application.

Applicant's arguments

Applicant argues that Povey et al cannot be used in the context that the Examiner is using it. The modification made in that reference is made solely to change the properties of the packaging cell and not the viruses that emanate from it. There is simply nothing here that says one way or the other whether the SCF on the packaging cells is incorporated into the virus

Applicant argues that Hammarstedt et al. only relates to membrane proteins that are endogenously expressed cellular components. Therefore, Applicant argues that it cannot be predicted from this paper that expression of extra-genomic material will occur in such a way that it can be guaranteed that it will become incorporated in the virus that buds from such a modified cell. Although there is no reason to assume that such a protein will behave differently to an endogenous one but equally one cannot be sure of this either.

Response to Applicant's arguments

It is noted that Povey et al. teaches constructed *a retroviral producer line* (1MI-ΔSCF) that expresses the membrane-bound form of human stem cell factor (SCF) on its cell surface, which is the step required for the claimed methods regarding "expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane of the packaging cell" recited in step (ii) of claim 43. As Povey et al. teaches the same step of claimed methods, practicing the step taught by Povey et al. certainly anticipates the same consequences of the step pertaining to the limitation "a viral particle buds from said packaging cell membrane thereby allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity". Furthermore, this anticipation is further supported and evident by the teachings of Hammarstedt et al. regarding plasma membrane (PM) proteins become incorporated into the retrovirus envelope without significant sorting, and this feature of retrovirus assembly should be considered when studying retrovirus functions and developing retrovirus vectors. It is worth noting again that there is no requirement specified what "a first cell binding activity" is and how "a first cell binding activity" is modified.

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 43, 48, 50 and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Povey et al.** (Povey et al., Enhanced retroviral transduction of 5-fluorouracil-resistant human bone marrow (stem) cells using a genetically modified packaging cell line, *Blood*, 92(11):4080-9, 1998) in view of **Hammarstedt et al.** (Hammarstedt et al. Minimal exclusion of plasma membrane proteins during retroviral envelope formation. *Proc Natl Acad Sci U S A.* 97(13):7527-32, 2000) and **Dropulic et al.** (U.S. patent No. 6,114,141, issued Sep. 5, 2000; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006). Applicant's arguments filed 10/14/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 20-23 of the office action mailed on 04/14/2009.

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(ii) expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane of the packaging cell and a viral particle buds from said packaging cell membrane thereby allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity, wherein the passenger peptide binding moiety is selected from the group consisting of cell growth factors, antibodies or antigen-binding fragments thereof, moieties that recognize a target cell specific surface antigen, and moieties that are at least a part of a member of a binding pair comprising a target cell specific cell surface receptor and its ligand and wherein said passenger peptide is other than one naturally
derived from the virus or said packaging cell.

Claim interpretation: The limitation "wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety" reads on any extra-chromosomal nucleic acid introduced into a given viral packaging cell because extra-chromosomal nucleic acids are exogenous to the endogenous genomic DNA of the viral packaging cell.

Povey et al. teaches constructed a retroviral producer line (1MI-ΔSCF) that expresses the membrane-bound form of human stem cell factor (SCF) on its cell surface (See bridging paragraph, pages 4081-4082, and Figure 1, provided below, Povey et al., *Blood*, 92(11):4080-9, 1998).

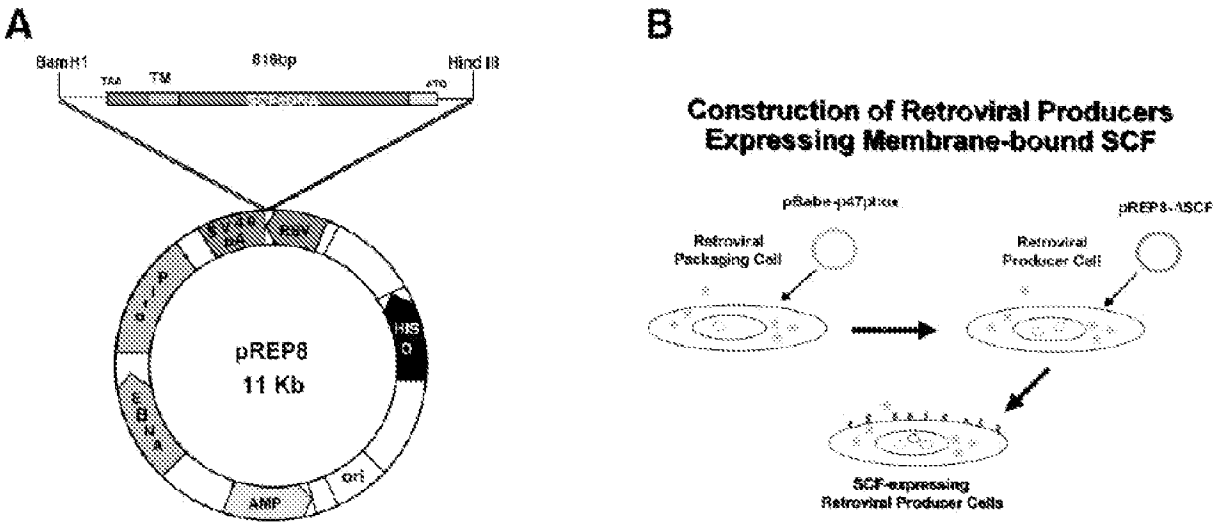

Fig 1. Construction of retroviral producer cells expressing membrane-bound SCF. (A) Schematic of plasmid pREP8-ΔSCF. (B) Evolution of cell line 1MI-ΔSCF from AM12 packaging line.

Povey et al. the retroviral transduction frequency of the quiescent 5-fluorouracil (FU) resistant bone marrow cells using the SCF-expressing producer line averaged about 20%, whereas those transduced using the retroviral particle obtained from parent producer line showed evidence of reduced levels or no transduction (See page 4084 and Figure 3, Povey et al., *Blood*, 92(11):4080-9, 1998).

Povey et al. does not explicitly teach that the SCF (i.e. a passenger peptide binding moiety encoded by exogenous nucleic acid recited in claim 43 of instant application) is allowed to be incorporated into the viral particle, which in turn may account, at least in part, for the increased retroviral transduction frequency using the SCF-expressing producer line.

However, Hammarstedt et al. teaches that the retrovirus forms its envelope by budding at the plasma membrane (PM), and this process is primarily driven by its cytoplasmic core-precursor protein, Gag, as shown by the efficient formation of virus-like Gag particles in the absence of its envelope protein, Env. Hammarstedt et al. teaches the purification of Moloney murine leukemia virus Gag particles by sedimentation in an iodixanol gradient and donor PMs

by flotation in a sucrose gradient and compared their protein compositions at equal lipid basis, and found that most PM proteins are present at similar density in both membranes. Hammarstedt et al. teaches the inclusion of PM proteins was unaffected by incorporation of Env protein into the envelope of the Gag particles and whether these were produced at high or low level in the cells. Hammarstedt et al. concludes that these findings indicate that most PM proteins become incorporated into the retrovirus envelope without significant sorting, and this feature of retrovirus assembly should be considered when studying retrovirus functions and developing retrovirus vectors.

The teachings by Hammarstedt et al. indicates that the retroviral particles produced from the SCF-expressing producer line taught by **Povey et al.** inherently allow the SCF, expressed on the plasma membrane of the retroviral packaging cell, to be incorporated into the retroviral particles when the viral particle buds from the retroviral packaging cell, as recited in claim 43 of instant application.

Neither Povey et al. nor Hammarstedt et al. teaches additional nucleic acid which can express any one of the bioactive agent selected from ricin, tumor necrosis factor, interleukin-2 (a cytokine), interferon-gamma, ribonuclease, deoxyribonuclease, pseudomonas exotoxin A and caspase.

With regard to claim 43, 48, 50 and 51, Dropulic et al. teach methods to express genes from viral vectors (See title and abstract). Specifically, Dropulic et al. teach the expression of antiviral agent including a cytokine, a single-chain antibody, a cellular antigen or receptor (See claims 4 and 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Dropulic et al. regarding expressing a cytokine (interleukine-2) from a viral vector into the combined teachings of Povey et al. and Hammarstedt et al. regarding the method of generating a retrovirus with altered tropism and to achieve the claim 51 of instant application on a method of making a viral particle having a modified cell binding activity and also expressing a bioactive agent including interleukin-2.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Povey et al. and Hammarstedt et al. to express antiviral agent interleukin-2 by the teachings of Dropulic et al. to achieve the goal of site specific delivery of interleukin as an antiviral agent via the selection of altered tropism of viral particle.

There would have been a reasonable expectation of success given (1) the generation of viral particle with altered tropism resulting from accelerated evolution of envelope genes by the teachings of Povey et al. and Hammarstedt et al., and (2) the expression of a cytokine from a viral vector by the teachings of Dropulic et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that applicant has adequately demonstrated significant differences between any combination of Hammarstedt et al with Povey et al with regard to the present claims and Applicant believes that Dropulic et al does not introduce any teaching or suggestion that overcomes the deficiency of those references and, therefore, applicant believes his claims to

patentably distinguish over this combination and, this being the case, he requests that the Examiner reconsider and withdraw this rejection. Applicant states that the same conclusion can adequately be applied to the rejection of claims 43, 48, 52 and 53 under 35 USC § 103(a) based on Povey et al., Hammarstedt et al., and Dropulic et al.

Response to Applicant's arguments

As responded in the maintained rejection of claims 43-45, 47, and 54-56 under 35 U.S.C. 102(b) as being anticipated by Povey et al. (*Blood*, 92(11):4080-9, 1998) as evidenced by Hammarstedt et al. (*Proc Natl Acad Sci U S A.* 97(13):7527-32, 2000), Povey et al. teaches the step "expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane of the packaging cell" recited in step (ii) of claim 43, thereby, practicing the step taught by Povey et al. certainly anticipates the same consequences of the step pertaining to the limitation "a viral particle buds from said packaging cell membrane thereby allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity". Dropulic et al. is relied on for the teachings on nucleic acid which can express any one of the bioactive agent selected from ricin, tumor necrosis factor, interleukin-2 (a cytokine), interferon-gamma, ribonuclease, deoxyribonuclease, pseudomonas exotoxin A and caspase, recited in claim 43, 48, 50 and 51 of instant application.

6. Claims 43, 48, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Povey et al.** (Povey et al., Enhanced retroviral transduction of 5-fluorouracil-resistant human bone marrow (stem) cells using a genetically modified packaging cell line, *Blood*, 92(11):4080-

9, 1998) in view of **Hammarstedt et al.** (Hammarstedt et al. Minimal exclusion of plasma membrane proteins during retroviral envelope formation. *Proc Natl Acad Sci U S A.* 97(13):7527-32, 2000) and **Guber et al.** (U.S. patent No. 569,177, issued Nov. 25, 1997; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006). Applicant's arguments filed 10/14/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 23-27 of the office action mailed on 04/14/2009.

For the clarity and completeness of this office action, the rejection is ***maintained*** for the reasons of record advanced on pages 23-27 of the office action mailed on 04/14/2009, is reiterated below with editorial revisions addressing claim amendments filed on 10/14/2009.

Amended claim 43 filed on 10/14/2009 reads as follows: A method of making a viral particle having a modified cell binding activity comprising:

(i) providing a viral packaging cell containing viral nucleic acid encoding an enveloped viral particle, wherein said viral particle is enveloped using an envelope unable to naturally bind to cells of a species being targeted, said viral particle having a first cell binding activity wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety designed to modify said first cell binding activity of said viral particle;

(ii) expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane of the packaging cell and a viral particle buds from said packaging cell membrane thereby allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity, wherein the passenger peptide binding moiety is selected from the group consisting of cell growth factors, antibodies or antigen-binding fragments thereof, moieties that recognize a target cell specific surface antigen, and moieties that are at least a part of a member of a binding pair comprising a target cell specific cell surface receptor and its ligand

and wherein said passenger peptide is other than one naturally derived from the virus or said packaging cell.

Claim interpretation: The limitation "wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety" reads on any extra-chromosomal nucleic acid introduced into a given viral packaging cell because extra-chromosomal nucleic acids are exogenous to the endogenous genomic DNA of the viral packaging cell.

Povey et al. teaches constructed a retroviral producer line (1MI-ΔSCF) that expresses the membrane-bound form of human stem cell factor (SCF) on its cell surface (See bridging paragraph, pages 4081-4082, and Figure 1, provided below, Povey et al., *Blood*, 92(11):4080-9, 1998).

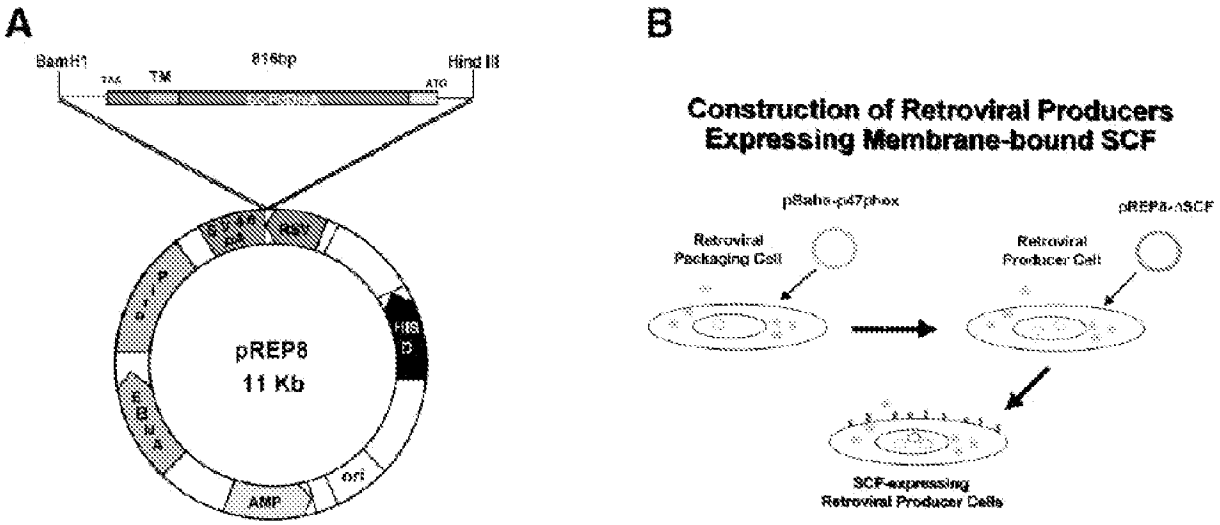

Fig 1. Construction of retroviral producer cells expressing membrane-bound SCF. (A) Schematic of plasmid pREP8-ΔSCF. (B) Evolution of cell line 1MI-ΔSCF from AM12 packaging line.

Povey et al. the retroviral transduction frequency of the quiescent 5-fluorouracil (FU) resistant bone marrow cells using the SCF-expressing producer line averaged about 20%, whereas those transduced using the retroviral particle obtained from parent producer line showed

evidence of reduced levels or no transduction (See page 4084 and Figure 3, Povey et al., *Blood*, 92(11):4080-9, 1998).

Povey et al. does not explicitly teach that the SCF (i.e. a passenger peptide binding moiety encoded by exogenous nucleic acid, encompassed by claim 43 of instant application) is allowed to be incorporated into the viral particle, which in turn may account, at least in part, for the increased retroviral transduction frequency using the SCF-expressing producer line.

However, Hammarstedt et al. teaches that the retrovirus forms its envelope by budding at the plasma membrane (PM), and this process is primarily driven by its cytoplasmic core-precursor protein, Gag, as shown by the efficient formation of virus-like Gag particles in the absence of its envelope protein, Env. Hammarstedt et al. teaches the purification of Moloney murine leukemia virus Gag particles by sedimentation in an iodixanol gradient and donor PMs by flotation in a sucrose gradient and compared their protein compositions at equal lipid basis, and found that most PM proteins are present at similar density in both membranes. Hammarstedt et al. teaches the inclusion of PM proteins was unaffected by incorporation of Env protein into the envelope of the Gag particles and whether these were produced at high or low level in the cells. Hammarstedt et al. concludes that these findings indicate that most PM proteins become incorporated into the retrovirus envelope without significant sorting, and this feature of retrovirus assembly should be considered when studying retrovirus functions and developing retrovirus vectors.

The teachings by Hammarstedt et al. indicates that the retroviral particles produced from the SCF-expressing producer line taught by **Povey et al.** inherently allow the SCF, expressed on the plasma membrane of the retroviral packaging cell, to be incorporated into the retroviral

particles when the viral particle buds from the retroviral packaging cell, as recited in claim 43 of instant application.

Neither Povey et al. nor Hammarstedt et al. teaches additional nucleic acid which can express any one of the bioactive agent, which is an enzyme, including thymidine kinase and cytosine deaminase, capable of converting a relatively non-toxic pro-drug into a cytotoxic drug.

With regard to claims 43, 48, and 52-53, Guber et al. teach recombinant retroviruses expressing a protein that converts a pro-drug into a cytotoxic agent (See title and abstract). Specifically, Guber et al. teaches the expression of a nucleoside kinase thymidine kinase (See claims 6-8, 22-23) that converts a purine-based or pyridimine-based drug with little or no cytotoxicity into a cytotoxic drug (See claim 5)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Guber et al. to express a thymidine kinase that converts a pro-drug into a cytotoxic drug into the combined teachings of Povey et al. nor Hammarstedt et al. regarding the method of generating a retrovirus with altered tropism and to achieve the claims 52 and 53 of instant application regarding a method of making a retroviral particle having a modified cell binding activity and also expressing a bioactive agent such as thymidine kinase capable of converting a relatively non-toxic pro-drug into a cytotoxic drug.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Povey et al. and Hammarstedt et al. to express thymidine kinase by the teachings of Guber et al. to achieve the goal of site specific delivery of thymidine kinase to a desired cell target for converting a pro-drug into a cytotoxic drug via the binding specificity of altered tropism of virus as taught by Povey et al. nor Hammarstedt et al.

There would have been a reasonable expectation of success given (1) the generation of viral particle with altered tropism resulting from accelerated evolution of envelope genes by the teachings of Povey et al. and Hammarstedt et al., and (2) the expression of thymidine kinase converting a pro-drug into a cytotoxic drug from a recombinant retroviral vector by the teachings of Guber et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Examiner's ***Response to Applicant's arguments*** are the same as documented in the maintained rejection of claims 43, 48, 50 and 51 under 35 U.S.C. 103(a) as being unpatentable over Povey et al. (*Blood*, 92(11):4080-9, 1998) in view of Hammarstedt et al. (*Proc Natl Acad Sci U S A*. 97(13):7527-32, 2000) and Dropulic et al. (U.S. patent No. 6,114,141, issued Sep. 5, 2000). It is noted that Guber et al. is relied on for the teachings on additional nucleic acid which can express any one of the bioactive agent, which is an enzyme, including thymidine kinase and cytosine deaminase, capable of converting a relatively non-toxic pro-drug into a cytotoxic drug, recited in claims 43, 48, 52, and 53.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632